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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/373,018	08/11/99	NASH H	10845/014002

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EXAMINER	
MORAN, M	
ART UNIT	PAPER NUMBER
1631	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Acti n Summary	Application No. 09/373,018	Applicant(s) NASH ET AL.	
	Examin r Morjorie Moran	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-22 and 51-72* is/are pending in the application.

4a) Of the above claim(s) *54-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-22 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 and 12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

El ction/Restrictions

Applicant's election with traverse of Group I, claims 16-22 and 51-53, in Paper No. 15, filed 3/30/01, is acknowledged. The traversal is on the ground(s) that the method of Group II incorporates the steps of Group I and is, in essence, the method of Group I performed in an iterative fashion. This is not found persuasive because, as previously set forth in the restriction requirement of 2/12/01, the method of Group II recites different method steps and requires use of products not required in the method of Group I. The method of Group I can be practiced without regard to the steps or results of Group II. In addition, a search for the method steps of Group I is not contiguous with a search for the method steps of Group II; a search for the method of Group II requires a search for method steps and materials not required in a search for the method steps and products of Group I. In response to the argument that the method steps of Group II are the steps of Group I performed in an iterative fashion, it is noted that an "iterative" method of screening a combinatorial library is generally regarded in the art as one which iteratively screens a library, and subsections thereof, against the SAME biomolecule in order to find members of the library which are the "best" ligands, inhibitors, etc. for that biomolecule (i.e. which bind most avidly, give the highest inhibition, etc.) See e.g. REBEK et al. (IDS ref, WO 9519359, pages 70-71). A subtractive method such as that recited in Group II (wherein the results from binding to one biomolecule are "subtracted" from the results of binding to a different biomolecule) is not generally considered an iterative method of screening. It is noted that a similar method of subtractive screening, reciting the same method steps as claim 54, was recited as an independent claim in original claim 34. The requirement is still deemed proper and is therefore made FINAL.

In a response filed 8/17/01, applicant also traversed an election of species requirement by arguing that the election of "amine" as a peripheral moiety precursor was intended to mean compounds comprising an amine group, as set forth in Example 1 on page 20 of the instant specification. Given this argument, the examiner interprets applicant's election of a peripheral moiety precursor to be a compound which "includes a primary or secondary amino group which reacts with the scaffold precursor to form an amide" as disclosed in lines 3-8 on page 20. Applicant also elected a fused ring system as a scaffold precursor and an acid chloride as the reactive group on the scaffold precursor, and a protein as the biomolecule in the response filed 3/30/01. Applicant did not set forth any arguments with respect to election of a scaffold precursor, reactive group, or biomolecule, therefore election of these species is considered to be without traverse.

Claims 54-72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 15.

An action on the merits of claims 16-22 and 51-53, as they read on elected species set forth above, follows.

Priority

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, e.g. "This application is a divisional of 09/024,592, filed February 17, 1998, now Patent No. 6,207,861, and claims priority to 60/070,456, filed January 5, 1998."

Information Disclosure Statement

The Supplemental IDS's (Forms 1449) filed 12/17/99 (paper # 4) and 12/4/00 (paper #12) have been considered in full. All references on the IDS (Form 1449) filed 12/17/99 (paper # 3) have been considered EXCEPT reference CJ on page 3. Reference CJ cites both a Chemical Abstracts Accession number and a PCT document number, but does not specify whether the abstract (only) or the PCT document (in full) was submitted for consideration. No reference (e.g. abstract) corresponding to the Chemical Abstracts Accession number was found in either the instant application or its parent application. WO 9708190 (the PCT document) is cited separately and the full document was found in the parent application. Citation AD on page 1 has been initialed to indicate that the entire PCT document has been considered. Citation CJ on page 3 has been crossed out to indicate that it has not been considered.

Drawings

The drawings are objected to by the Draftsperson as set forth on Form PTO948. The following is a reminder of the rules regarding drawing changes:

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set forth for response to this Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

Claim Objections

Claim 53 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 53 limits peripheral moiety precursors which react with a scaffold precursor to be members of a single peripheral moiety precursor subset. Parent claim 16 recites "reacting a scaffold precursor ... with a peripheral moiety precursor subset". Use of the term "a" in claim 16 implies a single peripheral moiety precursor subset. Members of the peripheral moiety precursor subset which react with the scaffold precursor in claim 16 are necessarily members of that single subset, therefore claim 53 does not further limit the method of parent claim 16.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-22 and 51-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16 and 51 recite the phrase "at least about" in lines 13 and 1, respectively. Use of this phrase makes it unclear what applicant intends as a lower limit for his number of combinations, therefore the claims are indefinite. This rejection may be overcome by deleting "about" in each claim, if such an amendment is consistent with applicant's intent.

Claim 16 recites a method of screening a mass combinatorial library which comprises steps (a) through (d). Claim 16 also limits the mass combinatorial library to be "produced by" a reaction between a scaffold precursor and a peripheral moiety precursor subset. It is unclear if the "production" steps are intended to be method steps in the screening method, therefore the claim is indefinite. If applicant intends the method of producing a mass combinatorial library to be a limitation of the claimed method of screening, then the examiner recommends reciting the production steps as active method steps, similar to screening steps (a) through (d). Applicant should note that a product produced by a particular process is not limited to the manipulations of the recited steps of the process, only the structure implied by the steps (see MPEP 2113).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16-19, 22 and 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by REBEK et al. (IDS ref; WO 9519359).

REBEK teaches a method of identifying a member or members of a mass-coded combinatorial library (hereinafter "library") which is a ligand for a biomolecule, specifically Con A

(a protein), by contacting Con A bound to a Sepharose support with the library to allow library members which are ligands of Con A to form Con A/ligand complexes, washing away unbound members of the library, dissociating and eluting the bound members, and analyzing the eluted members of the library (pp. 66-68, Example 6). REBEK teaches that his method of analysis is identification of library members by molecular mass analysis (p. 70, Example 9). REBAK teaches that his library is one produced by reacting xanthene tetra-acid chloride (a scaffold precursor comprising a fused ring system and chloride reactive groups) with tool molecules (i.e. peripheral moiety precursors) comprising an amine group (a subset of possible "tool groups") such that the library may comprise over 97,000 different molecules (p. 55). As REBEK's library therefore comprises compounds of the general formula XYn wherein X is the scaffold and Y is the peripheral moiety and n is the number of peripheral moieties attached to the scaffold (taught by REBEK to be four), claims 16-17 and 22 are anticipated. REBEK teaches that his affinity matrix (e.g. Con A attached to Sepharose) may be contained in a column (p. 67, first 3 lines), thereby anticipating claim 18. REBEK also teaches solution-phase assays (pp. 68-69, Example 7), thereby anticipating claim 19. REBEK further teaches that subsets of larger libraries may be screened wherein the structure of each member of the subset may be identified according to its molecular weight (p. 71), thus teaching screening of a subset wherein at least 90% of the combinations of peripheral moieties derived from the subset (i.e. library molecules produced from the subset of peripheral moiety precursors) have molecule mass sums distinct from the molecule mass sums of the other members of the library produced from the subset, and anticipating claim 51. The reactive groups on REBEK's scaffold molecule are all chlorides and are therefore all capable of reacting with the amine-containing "tool molecules" (peripheral moiety precursors) of REBEK. In addition, the peripheral moiety precursors of REBEK all

comprise a single amine reactive group and are therefore members of a single peripheral moiety precursor subset, therefore claims 52-53 are anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16-20, 22, and 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over REBEK et al. (IDS ref; WO 9519359) in view of HSIEH et al. (IDS ref; Molec. Diversity (1996) vol. 2, pages 189-196).

Claim 16 recites a method of identifying a member of a mass coded combinatorial library which is a ligand for a first biomolecule wherein the biomolecule is contacted with the library and a complex allowed to form, unbound members of the library are separated from the complex, the complex dissociated, and the identity of the dissociated members of the library (i.e. ligands) identified by determination of the molecular mass of each ligand. Claim 16 further limits the

library to one which is produced by reaction of a scaffold comprising n reactive groups with a peripheral moiety precursor subset such that at least 250 distinct combinations result. Claims 17-18 limit the biomolecule to be immobilized on a solid support, specifically a water-insoluble matrix in a chromatographic column. Claim 19 limits the biomolecule to be comprised in a solution which is contacted with the library to form a solution comprising biomolecule-ligand complexes and unbound library members. Claim 20 limits the method of claim 19 to one wherein unbound members of the library are separated from biomolecule-ligand complexes with a size-exclusion chromatography column. Claim 22 limits the biomolecule to a protein. Claim 51 limits the method to one wherein 90% of the combinations in the library (formed by reaction of peripheral moiety precursors with the scaffold precursor) have molecular mass sums distinct from the molecular mass sums of any other combinations in the library. Claim 52 limits the n reactive groups of the scaffold to ones which are contacted by and able to react with members of the "same" peripheral moiety precursor subset. Claim 53 limits the peripheral moiety precursors of claim 16 to be members of a single subset.

REBEK teaches a method of identifying members of a library which are ligands of a biomolecule, specifically Con A, as set forth above. REBEK teaches that his library is formed by reaction of a fused ring scaffold comprising four chloride reactive groups (xanthene-tetra-acid-chloride) with a peripheral moiety precursor subset comprising amine groups, wherein all members of the peripheral moiety precursor are members of the same subset (i.e. all comprise a single reactive amine group), and wherein all of the chloride groups on the scaffold are able to react with the amines, as set forth above. REBEK further teaches that members of his library may bind to a protein which is immobilized on Sepharose in a column, or may bind in solution, and teaches that nonbound members of the library may be washed away from bound members (ligand-biomolecule complexes), then dissociated and identified by mass, as set forth above.

REBEK does not teach separation of unbound library members from ligand-biomolecule complexes using a size-exclusion chromatography column.

HSIEH teaches identification of members of a small molecule library as ligands for target biomolecules by allowing complexes between the biomolecule and library members to form in solution, separating complexes from unbound library members by passing the mixture over a size-exclusion chromatography column, dissociating the complexes, and identifying the ligands by mass spectrometry (pp. 195, last paragraph-196).

It would have been obvious to one of ordinary skill in the art at the time of invention to have used the solution-phase binding and size-exclusion column chromatography of HSIEH to identify members of the library which are ligands for particular proteins in the method of REBEK where the motivation would have been to facilitate high-throughput identification of ligands and decrease the time to run the method by using a fully automated procedure, as taught by HSIEH (p. 195, right column). One skilled in the art would reasonably have expected success in using the solution-phase binding and size-exclusion column chromatography of HSIEH to identify members of the library which are ligands for particular proteins in the method of REBEK because REBEK teaches that his method may be a solution-phase method and both REBEK and HSIEH teach methods to identify which members of a library are protein ligands.

Claims 16-19, 21-22, and 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over REBEK et al. (IDS ref; WO 9519359) in view of BREEMAN et al. (IDS ref; Anal. Chem. (1997)).

Claim 16 recites a method of identifying a member of a mass coded combinatorial library which is a ligand for a biomolecule, as set forth above. Claim 19 limits the method to one performed in solution phase, as set forth above. Claim 21 limits the method of claim 19 to one

wherein unbound library members are separated from ligand-biomolecule complexes using a size-exclusion membrane.

REBEK teaches a method of identifying members of a library which are ligands of a molecule, specifically Con A, as set forth above. REBEK does not teach use of a size-exclusion membrane.

BREEMAN teaches identification of members of a library which are ligands for an enzyme wherein the enzyme and library members are allowed to associate in solution in an ultrafiltration chamber, on one side of an ultrafiltration/size exclusion membrane, unbound library members are washed away (though the membrane), and bound members are dissociated from the enzyme and identified by mass spectrometry (p. 2163, left column).

It would have been obvious to one of ordinary skill in the art at the time of invention to have used the solution-phase binding and ultrafiltration separation of BREEMAN to identify members of the library which are ligands for a particular protein in the method of REBEK where the motivation would have been to allow concentration of ligands from a dilute solution and facilitate recovery and re-use of proteins, as taught by BREEMAN (p. 2164). One skilled in the art would reasonably have expected success in using the solution-phase binding and ultrafiltration separation of BREEMAN to identify members of the library which are ligands for a particular protein in the method of REBEK because both REBEK and BREEMAN teach identification of members of a library as ligands for a protein in solution phase.

Conclusion

Claims 16-22 and 51-53 are rejected. Claims 54-72 are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (703) 305-2363. The examiner can normally be reached on Monday to Friday, 7:30 am to 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (703) 308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to a patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Marjorie A. Moran
October 30, 2001